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Animal models of celiac disease. Usefulness and limitations.

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Introduction and Objective

Celiac disease is a chronic enteropathy caused by inappropriate immune response against peptides of gluten present in dryland cereals, mainly affecting genetically predisposed individuals who express HLA-DQ2 and HLA-DQ8, although gluten is also able to activate innate immunity. The lack of an animal model that reproduces completely the disease hinders the progress towards the research on the CD pathogenesis. Gluten intolerance is a very important public health problem because it is clearly a disease underdiagnosed.

The aim of this literature review is to find the most suitable animal model in order to clarify the disease pathogenesis process and to find new therapeutic targets.

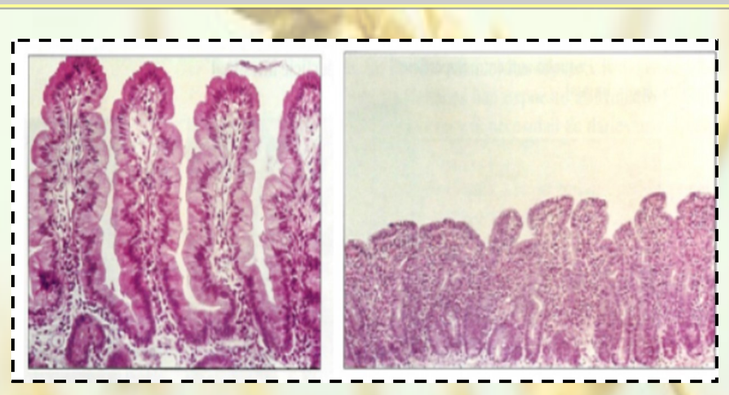

Figure 2. Normal duodenal mucosa of a CD control patient (A) and a patient with CD (B) showing villus atrophy and hiperplasia of the crypts. (Arranz E et al. *Inmunopatogenia de la enfermedad celiaca, 2012)*

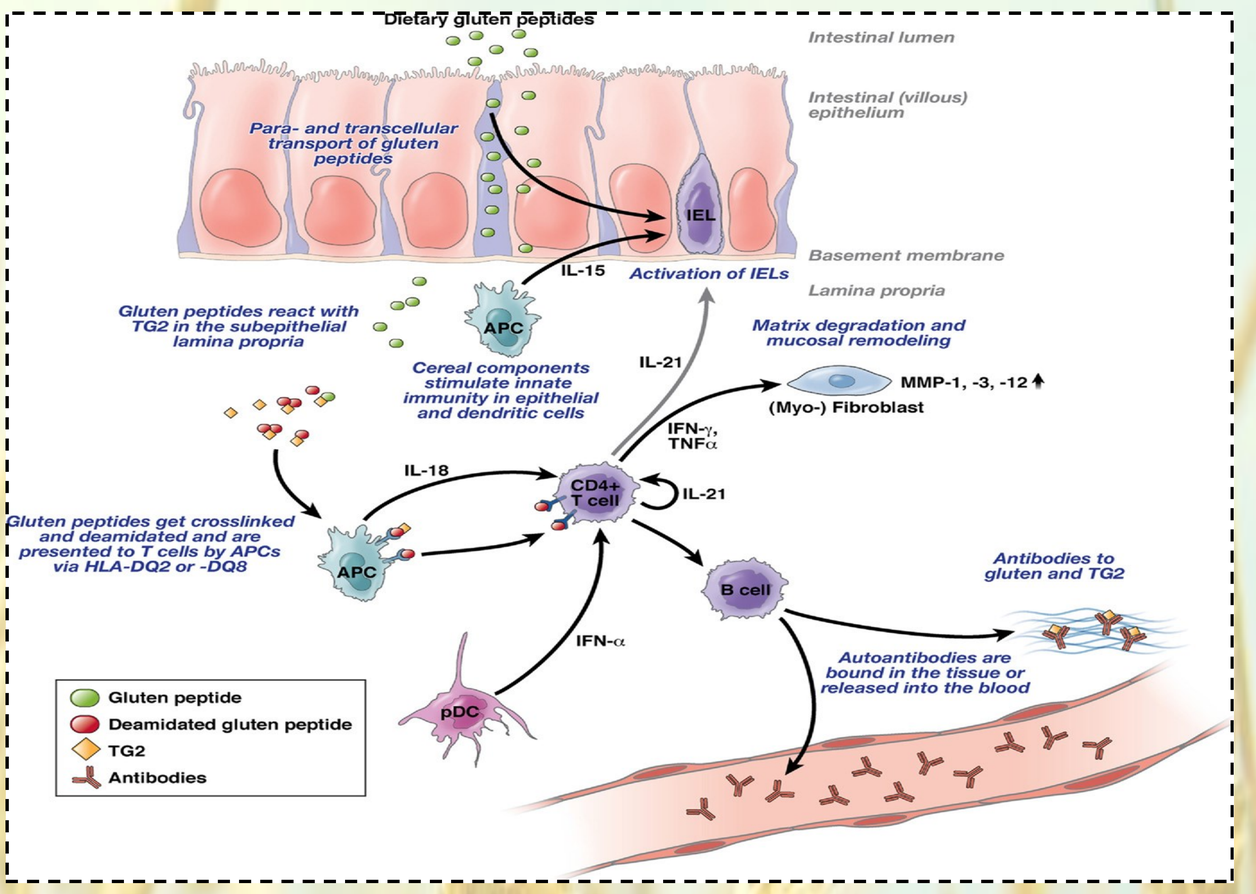

Figure 1. Immunopathogenesis of MHC-II dependent CD. The activation of T cells reactive to gluten in the small intestine triggers an inflammatory response dominated by Th1 cytokine profile, predominantly IFN- γ and other pro-inflammatory cytokines (TNF-α, IL-15) with proportional decline of immunoregulatory cytokines (IL-10, TGF-β). This imbalance causes histological changes at the level of the intestinal wall .

Therapeutic Approach

Gluten free-diet

Urgent need to develop safe and therapeutic alternatives:

1.**Use of probiotics and intestinal microbiota** to enhance the intestinal permeability.

2. Promote the function of the intestinal barrier: some drugs act protecting the integrity of the tight junctions in the small intestine.

3. Prevention of the formation of immunogenic peptides: using polymers that bind to gliadin preventing recognition of MHC-II.

4. Oral enzyme therapy: the prolyl-endopeptidases (PEP) are able to easily split immunostimulatory gluten peptides rich in proline. Identifity a gluten threshold dose well tolerated by most patients when consuming a PEP specific dose.

5. Block the presentation of the peptide HLA.DQ.

6. Inhibitors of tissue transglutaminase (TG2) with activity limited towards the intestinal lining.

7. Blockade of gliadin transcellular transport.

8. Anti IL-15 and anti-IFN-γ neutralizing antibodies are promising candidates for future therapies.

9. NKG2D antagonists alters the growth and functions of reactive $CD8^+$ T cells.

Table 1. Animal models for the study of gluten sensitivity: Usefulness and limitations.

Species	Transgene	Small intestinal enteropathy	Enteropathy is gluten dependent	Protocol for induction of small intestinal enteropathy	Ab against gliadin	Ab against TG2	Villus atrophy	Crypt hyperplasia	IEL accumulation	MHCII dependent	Strategy tested
Spontaneous models											
Horse	n/a	yes	yes	Gluten containing diet	yes	yes	yes	unknown	unknown	unknown	
Rhesus macaque	n/a	yes	yes	Gluten containing diet	yes	yes	yes	yes	yes	unknown	Endoprotea
Irish setter dog	n/a	yes	yes	Gluten containing diet	yes	unknown	yes	unknown	yes	no	
Non-spontaneous models											
Wistar rat	n/a	yes	yes	Gliadin feed with i.p. injection of IFN-γ	unknown	unknown	yes	unknown	unknown	unknown	Probiotics
Mouse	Gliadin-primed T cells from C57BL/6 donor mice transferred in RAG1−/−	yes	yes	Injection of gliadin+CFA in tail base of donor mice and recipient mice on gluten containing diet	yes	no	yes	yes	yes	Yes (murine MHCII)	Germinated rye sourdough
Mouse	HLA DQ2x MHCII−/−	No	n/a	Injection of chymotrypsin-digested-gliadin+pertussis toxin i.p. followed by gluten containing diet	no	yes	no	no	no	Yes (HLA)	
Mouse	HLA DQ2x gliadinTCR	no	n/a	Injection of deamidated chymotrypsin-digested-gliadin+pertussis toxin i.p. followed by gluten containing diet (25) or Oral gavage with deamidated chymotrypsin-digested-gliadin (26)	unknown	unknown	no	no	no	Yes (HLA)	
Mouse	HLA DQ8 xMHCII−/−	yes	yes	Injection of crude gliadin+CFA i.p.or in footpad followed by gluten oral gavage	yes	unknown	no	unknown	yes	Yes (HLA)	Polymer, Larazotide acetate, non-wheat grains, probiotics
Mouse	NODxHLA DQ8	yes	yes	Weekly gavage with PT-digested-gliadin+cholera toxin	yes	yes	yes	yes	Only at the tip of the villus	Yes (HLA)	Polymer, TG2 inhibition-Elafin
Mouse	H2-D^d-IL-15Tg	yes	yes	5 gliadin feeds on alternate days	yes	yes	no	no	yes	Yes (HLA)	
Mouse	hIL-15Tge	yes	no	OVA containing diet	unknown	yes (irrespective of OVA [85])	yes	yes	yes	Yes (murine MHCII)	Tofacitinib, IL-15 blocking Ab

Final Conclusions

Transgenic animals are not the most appropriate model for CD, because they do not reflect reality. Instead, Macacus rhesus is the most suited model for spontaneous CD, but very few laboratories are approved by the ethics committee. New insights involving the swine SLA-II, particularly mutations into the SLA-DQA and SLA-DQB, point out the possibility of a new CD model, but more research efforts would be needed to elucidate its suitability. Actually, there is no animal model so far that encompasses all the features in order to study the CD, but further studies are needed to find an effective therapeutic strategy.